REMARKS

Rejection of Claims 1, 11-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-57, 60, 73-76, 78, 80-83 and 93-96 Under 35 U.S.C. § 103(a)

Claims 1, 8-13, 18, 22, 26, 31, 36, 40, 41, 46, 51, 55-60, 62-64, 73-83 and 93-97 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ponath *et al.* (WO 98/06248) in view of Gordon *et al.* (Reference AS5 of record) or Gordon *et al.* (Reference AT5 of record).

The Examiner maintains that Ponath *et al.* disclose treatment of ulcerative colitis with humanized LDP-02 antibody, wherein said antibody has the amino acid sequence recited in the claims. The Examiner further states that Ponath *et al.* disclose that the dosage and schedule of administration used would be determined using routine experimentation, that the antibody can be administered in multiple doses, and that the patient can additionally receive steroids or sulfasalazine or other immunosuppressive agents. The Examiner admits that Ponath *et al.* do not disclose the particular claimed administration protocols. (Office Action, pages 2-3).

The Examiner further maintains that the Gordon *et al.* references disclose that patients with inflammatory bowel disease or ulcerative colitis can be treated with a dose of 3 mg of humanized antibody against an α4 integrin, wherein said dosage is a starting point for future clinical studies. In the Examiner's opinion, a routineer would have started with the 3 mg/kg dosage disclosed by Gordon *et al.* and arrived at the claimed protocols using routine experimentation.

In response to Applicants' previous arguments in view of studies summarized by Feagan et al. (references AX5 and AY5 of record), the Examiner states that Feagan et al. disclose that it is unclear as to whether their antibody is actually preferable to the use of natalizumab for treatment of ulcerative colitis. (Office Action, page 5).

Applicants respectfully disagree. Although some scientists might have a desire to improve upon what is already generally known, one of ordinary skill in the art would not consider the dosage of an unrelated antibody as a starting point for which to begin testing a different antibody.

The combined teachings of Ponath *et al.* and the Gordon *et al.* references, at best, would provide a method for treating ulcerative colitis by administering an antibody at a single dose of 3 mg/kg. If, for arguments sake only, the person of skill in the art was motivated to use the dose of

3 mg/kg as a starting point for optimizing treatment within the disclosed range, the results would still be unpredictable and require undue experimentation.

Indeed, further experimental support of the claimed invention has been generated by the applicants. The experimental data addresses the Examiner's concerns regarding whether the antibody used in Feagan et al. (LDP-02) is actually preferable to natalizumab for treatment of ulcerative colitis. Two humanized antibodies, Humanized ACT-1 antibody, which binds α4β7-integrin heterodimer, and natalizumab, which binds molecules comprising α4-integrin, including α4β7-integrin and α4β1-integrin heterodimers, were compared in studies in non-human primates. As expected for the desired therapeutic effect, humanized ACT-1 antibody inhibited migration of lymphocytes to the gastrointestinal tract. However, not even high, multiple doses of humanized ACT-1 antibody could induce the systemic immunosuppression that was observed in primates treated with single, lower doses of natalizumab in these studies. A copy of an abstract (P-0144, Fedyk et al.) summarizing this study is included in the Supplemental Information Disclosure Statement filed concurrently.

A separate, integrated safety analysis was performed on data from nine clinical trials in healthy subjects and patients with inflammatory bowel disease (IBD). Overall 84% of subjects who received drug/treatment reported at least one adverse event (AE) compared to 87% placebo subjects. The Humanized ACT-1 Antibody was well-tolerated in all clinical trials to date with no increase in systemic infections and a possible trend in increased upper respiratory and mucosal infections. A copy of the abstract (P-0025, Feagan et al.) summarizing this study is included in the Supplemental Information Disclosure Statement filed concurrently.

Both experimental studies, summarized and filed concurrently herewith, rebut the Examiner's conclusion that it is unclear whether LDP-02 is in fact preferable to Natalizumab. Thus, the claimed invention is not obvious over the cited references because none of the references either individually or in combination suggest the claimed methods of treatment and the results of the method of treatment are unexpected.

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Acknowledgment of consideration of the references cited therein is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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